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Discriminative Stimulus Properties of Phencyclidine and Five Analogues in the Squirrel Monkey[1]

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BRADY, K. T. AND R. L. BALSTER. *Discriminative stimulus properties of phencyclidine and five analogues in the squirrel monkey.* PHARMAC. BIOCHEM. BEHAV. 14(2) 213–218, 1981.—Squirrel monkeys were trained to discriminate 0.16 mg/kg of 1-(1-phenylcyclohexyl) piperidine (PCP) from saline in a two-lever drug discrimination task on a fixed-ratio 32 schedule of food presentation. Intramuscular injections were given 5 min pre-session in a double alternation pattern. After reliable discriminative control of lever choice was established, dose-response determinations for generalization to the training dose of PCP were made with several doses of PCP, N-ethyl-1-phenylcyclohexylamine (PCE), 1-[1-(2-thienyl) cyclohexyl] piperidine (TCP), 1-(1-phenylcyclohexyl) morpholine (PCM), 1-(1-phenylcyclohexyl) pyrrolidine (PHP), and ketamine. All drugs produced dose-dependent PCP-appropriate responding. For each analogue, a dose was found which produced stimulus control of responding comparable to that of the PCP training dose. ED50 values were determined for each drug for percent drug-lever appropriate responding and for suppression of operant responding during test sessions. The relative potency for producing drug-lever appropriate responding was: TCP>PCP=PCE>PHP>PCM>ketamine. The relative potency for suppression of operant responding was: PCP=TCP>PHP>PCE>PCM>ketamine. In all cases, the dose necessary to suppress operant responding to fifty percent of vehicle rates was three to five times larger than the ED50 dose for drug-lever appropriate responding. The results of this study indicate marked similarities in the behavioral effects of these six arylcyclohexylamines.

Phencyclidine Phencyclidine analogues Squirrel monkeys Schedule-controlled behavior Drug discrimination

THE current escalation in the abuse of 1-(1-phenylcyclohexyl) piperidine (PCP) has brought an increasing amount of attention to the class of drugs to which it belongs, the dissociative anesthetics [4]. Some PCP analogues, most notably N-ethyl-1-phenylcyclohexylamine (PCE), 1-[1-(2-thienyl)cyclohexyl] piperidine (TCP), and 1-(1-phenylcyclohexyl)pyrrolidine (PHP), have already been discovered in illicit street use [27]. It is becoming apparent that a wide variety of structural modifications can be made in the PCP molecule without markedly altering its pharmacological profile. In order to better understand the pharmacology of this class of compounds, it would be helpful to determine the structural determinants of PCP-like activity.

A number of studies suggest pharmacological similarities between PCP and some of its analogues. Gehrmann and Killam [12] found that PCP, PCE, and 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone (ketamine) all produced similar EEG effects in rhesus monkeys. They found that PHP produced a qualitatively different EEG profile from the other analogues, and that 1-(1-phenylcyclohexyl) morpholine (PCM) was inactive in the dose range they tested. In another study in rhesus monkeys, Brady *et al.* [5] found that PCP, PCE, TCP and ketamine had qualitatively similar effects on fixed-interval performance.

Drug discrimination studies with this group of compounds suggest that PCP and some of its analogues also have similar discriminative stimulus properties. Jarbe *et al.* [15] and Overton [20] both reported that in a shock-escape T-maze, rats could be trained to discriminate PCP from saline. Jarbe and his associates found that ketamine and PCE generalized to PCP. Overton also found that ketamine generalized to PCP, but, in animals trained to perform a drug vs. drug discrimination task, it was demonstrated that PCP and ketamine could be discriminated from each other. Shannon [26], using rats trained in a 2-choice discrete trial avoidance task to discriminate PCP from saline, did generalization testing with a series of PCP analogues and other psychoactive drugs. He found that only the PCP analogues and the psychotomimetic

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opioid, N-allyl-nor-metazocine (SKF 10-047), produced a PCP-like cue. Poling *et al.* [25] tested a series of agonists and antagonists of several neurotransmitter systems for generalization to the PCP cue in rats trained to discriminate PCP from saline. The specificity of the PCP cue was again demonstrated in that only ketamine produced PCP-appropriate responding.

The present study was designed to compare the discriminative stimulus properties of PCP to those of PCE, TCP, PHP, PCM and ketamine (Fig. 1) in the squirrel monkey. There have been relatively few reports using the squirrel monkey as a subject in drug discrimination studies. It seems especially important to explore the discriminative stimulus properties of PCP in primates because of the apparent species-specificity of some of the pharmacological activities of this compound. The gross behavioral effects of PCP in man include ataxia, nystagmus and rhythmic movements [6,13]. These effects more closely resemble the effects of PCP in subhuman primates than its effects in rodent species [2, 3, 11].

METHOD

Subjects

The subjects were four experimentally naive adult male squirrel monkeys (*Saimiri sciureus,* Santa Cruz, Bolivia, Primate Imports, Port Washington, NY). The animals were maintained at 80% of free-feeding weights (0.8 to 1.0 kg) throughout the experiment by adjusted post-session feedings. They had unlimited access to water in their home cages.

Apparatus

The subjects were restrained about the waist in a plastic primate chair for the duration of the experimental session. In the lower center of the panel facing the subject seated in the chair was a brass food trough into which 97 mg Noyes banana-flavored food pellets could be delivered via a Gerbrands model D-1 automatic feeder. There were two response levers facing the subject equidistant to the right and left above the food trough. A clear Plexiglas divider with two arm holes was installed between the subject and the response levers. To reach a lever or the food trough the subject had to reach through the arm hole. The placement of the Plexiglas divider was such that the animal could press only one lever at a time. The purpose of this device was to prevent unwanted response topographies, and to force the animal to make a choice between the levers. Above the response panel were four stimulus lights.

The animal was injected while in the primate chair and the chair immediately placed in a sound and light attenuating isolation cubicle for the pretreatment time and the duration of the experimental session. The only source of light was the four stimulus lights above the levers which were illuminated at the initiation of the session. Solid state programming equipment and recording devices were located in an adjacent room.

Procedure

The subjects were trained to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty minute sessions were conducted seven days a week. Initially, the subjects were trained to respond on either lever on an FR1 schedule.

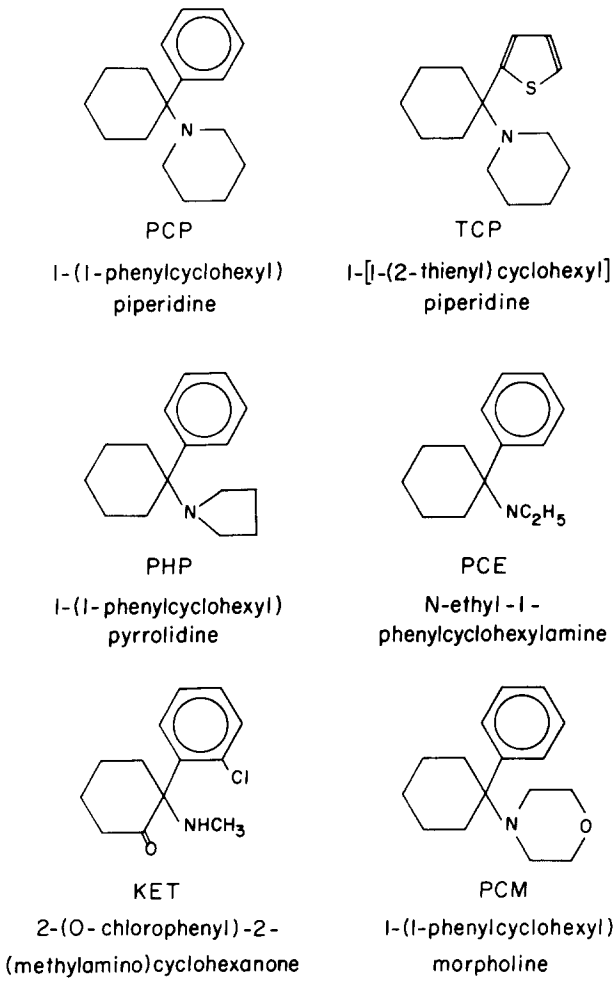

FIG. 1. Chemical structures of PCP and analogues.

Once lever pressing was established, drug injections were begun. Each animal received either saline or 0.16 mg/kg PCP 5 min pre-session on a double alternation schedule, i.e. two days of PCP injections followed by two days of saline injections. From this point on, responding on only one lever was reinforced during the session. For two animals, responses on the left lever produced reinforcement on PCP days and responses on the right lever produced reinforcement on saline days. The lever conditions were reversed for the other two subjects. Responses on the incorrect lever reset the FR contingency for reinforced responding on the correct lever. Response requirements were gradually increased until all animals reliably responded under an FR32 schedule.

When reliable FR32 responding was established, extinction probes were initiated. Every third session was begun with a 2 min period during which responding was not reinforced, after which the session was continued as usual on the FR32 schedule. Discrimination training was continued until the subject had ten consecutive extinction periods with 80% or more responding on the appropriate lever.

Following discrimination training, the effects of substitut-

ing 0.02, 0.04, 0.08, 0.24, 0.32 and 0.4 mg/kg doses of PCP for the 0.16 mg/kg training dose were determined. Two animals received the doses in ascending order, and two animals received the doses in descending order. The four middle doses were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day. Test sessions were conducted only if the animal completed the first fixed-ratio on the appropriate lever on the control day preceding the test day. The test session consisted of a 2 min extinction period after which the animals were returned to their cages. The double alternation continued on control days with the test sessions interspersed such that one PCP and one saline training day preceded each successive test day.

Following the PCP dose-response determination, stimulus generalization testing was conducted in a similar manner with six doses of ketamine (0.2–4.0 mg/kg), PHP (0.02–0.4 mg/kg), PCE (0.02–0.4 mg/kg), TCP (0.02–0.4 mg/kg) and PCM (0.2–4.0 mg/kg). These doses were chosen to cover a range from no effect to marked suppression of response rates during the 2 min test sessions. For each animal tested, two determinations were made of the four middle doses of each drug. In one animal, a seventh dose of PCE (0.48 mg/kg) was tested in order to determine a dose which completely suppressed responding.

The order in which the different drugs were given to each animal was randomized. All doses of a given drug were administered to a given subject before testing the next drug. For PCE and ketamine, two animals received each drug in ascending dose order, and two animals received each drug in a descending dose order. Only three subjects were tested with TCP, PHP, and PCM. For PCM and TCP, two animals received the drugs in a descending dose order and one animal received the drug in an ascending dose order. For PHP, two animals received the drug in an ascending dose order, and one animal received the drug in a descending dose order.

Drugs

PCP was supplied by Bio Ceutic Laboratories (Sernylan). Ketamine HCl was supplied by Parke-Davis Company (Ketalar). PCE, TCP, PHP and PCM were supplied by the National Institute on Drug Abuse. The drugs were diluted with or dissolved in sterile saline to a concentration that resulted in an injection volume of 0.2 ml/kg. All injections were given IM 5 min presession. Doses refer to the hydrochloride salts. Vehicle injections were 0.2 ml/kg of 0.9 percent saline.

Data Analysis

The overall response rates for total responses on both levers as well as the proportion of responses on the PCP-appropriate lever were calculated from responding on test days. For each drug, a saline test session conducted at the end of the drug dose-response determination was used to calculate vehicle response rates and percent PCP-lever responding after vehicle administration for that drug. Percent drug-lever responding was determined by dividing the number of PCP-lever appropriate responses made during the test period by the total number of responses made during that time and multiplying by 100. The effective dose 50% (ED50) for each drug was determined by least squares linear regression analysis using the dose-response data for percent drug-lever responding and the descending limb of the dose-response data for percent of vehicle response rates.

One sample t-tests ($\alpha \leq 0.05$) were carried out comparing the percent of baseline response rate following the administration of the three lowest doses of each drug tested with a hypothesized mean of 100 percent of baseline. Comparisons were made for each drug individually at all three doses in all animals as well as testing the effect of the lowest doses of all drugs in all animals grouped together. A two sample paired t-test ($\alpha \leq 0.05$) was carried out comparing the percent drug-lever appropriate responding following a saline training day to the percent drug-lever appropriate responding following a PCP training day for the four middle doses of each drug which were tested twice in each animal.

RESULTS

The training dose of PCP (0.16 mg/kg) produced approximately 85% drug-lever appropriate responding (Fig. 2, upper left panel). Higher doses of PCP produced an even higher percentage of drug-lever appropriate choices. At the 0.08 mg/kg dose of PCP, the animals made approximately 78% drug-lever appropriate choices without any significant decrease in response rate. All five analogues produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Fig. 2). At some doses, each of the analogues produced stimulus control of responding comparable to or greater than that of the PCP training dose. For all six compounds, the slopes of the lines for percent drug-lever appropriate responding were similar (Table 1). For those drug doses that were tested twice, there was no significant difference ($p \geq 0.05$) between the percent drug-lever appropriate responding for the test days following saline training days and the test days following PCP training days.

Overall response rates for each animal remained fairly stable throughout the experiment. Average values ± S.E.M. in responses per second for the response rates on vehicle test days for each animal were : 0.64 ± 0.03, 1.9 ± 0.22, 1.87 ± 0.13 and 2.1 ± 0.31. The effect of PCP and the analogues on overall response rate was often biphasic. Mean response rate increases over vehicle control rates were frequently seen with low doses of each drug (Fig. 2). T-tests making individual comparisons between the percent of vehicle responding produced by the three lowest doses of each compound and a null hypothesis mean of 100% failed to indicate that these response rate increases were significant ($p \geq 0.05$). T-tests comparing the percent of vehicle responding for the lowest doses of all drugs tested grouped together to the 100% null hypothesis also showed no significant difference ($p \geq 0.05$). Higher doses of all six compounds produced a dose-dependent decrease in response rate. At the higher drug doses some animals did not respond at all.

Table 1 shows the average ED50 values for suppression of operant responding and for percent drug-lever responding for each of the six compounds tested. The relative potency for producing drug-lever appropriate responding was: TCE>PCP=PCE>PHP>PCM>Ketamine. The relative potency for suppression of operant responding was: PCP=TCP>PHP>PCE>PCM>Ketamine. In all cases, the dose necessary to suppress operant responding to 50 percent of vehicle rates was three to five times larger than ED50 dose for drug-lever appropriate responding.

For all six compounds, similar observable effects after administration of high doses were noted when the animals were removed from the experimental chamber at the end of

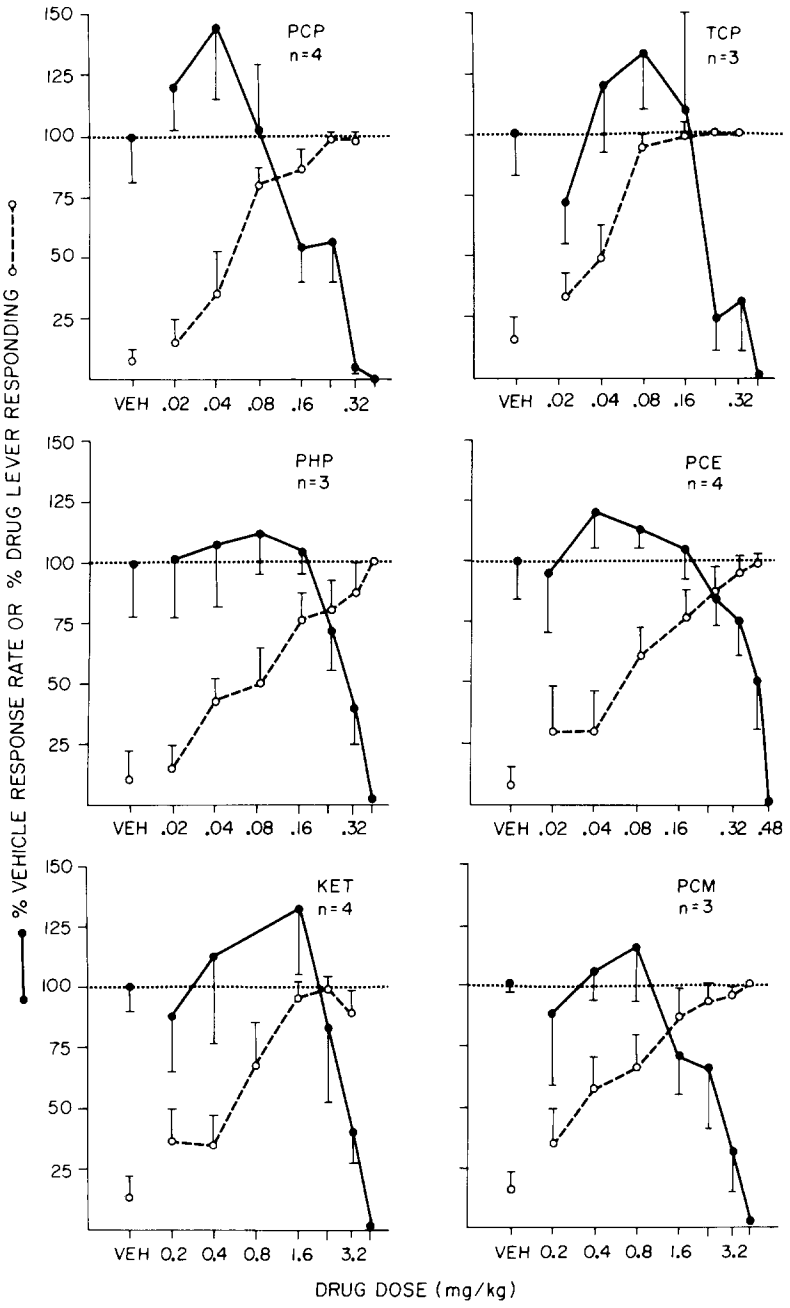

FIG. 2. Group dose-response curves for PCP and five analogues for suppression of operant responding and for percent drug-lever appropriate responding. The percent of vehicle response rate ± SEM averaged across animals (●——●) and the percent drug lever responding ± SEM averaged across animals (○---○) are on the ordinate with the corresponding drug dose on the abcissa. Vehicle rates were averaged for the two minute test session with saline pretreatment at the end of each drug dose-response determination for all animals tested with that day. The number of animals tested with each drug is indicated in each panel. Only one animal was tested with 0.48 mg/kg PCE.

TABLE 1

POTENCY OF PCP AND FIVE ANALOGUES FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATE IN SQUIRREL MONKEYS

Drug	ED50 Dose (mg/kg) Response Rate Suppression*	Ratio to PCP	Slope†	ED50 Dose (mg/kg) Drug Lever Responding‡	Ratio to PCP	Slope†	Ratio of ED50 Response Rate Suppression to ED50 Drug-Lever Responding
PCP	0.16		−0.01	0.055		0.01	2.9
TCP	0.16	1.0	−0.01	0.036	0.65	0.01	4.4
PHP	0.2	1.25	−0.01	0.07	1.3	0.02	2.9
PCE	0.28	1.75	−0.01	0.058	1.1	0.02	4.8
PCM	1.29	8.1	−0.01	0.37	6.73	0.02	3.5
KET	1.5	9.4	−0.01	0.48	8.7	0.02	3.1

*Dose resulting in a 50% decrease in response rates as determined by linear regression.
†In log10 dose (mg/kg)-percent units.
‡Dose resulting in 50% drug-lever responding as determined by linear regression.

the test session. These include excessive salivation, nystagmus and ataxia.

DISCUSSION

The results of this experiment indicate that all five analogues tested have discriminative stimulus properties similar to those of PCP. All five analogues produced PCP-appropriate responding in a dose-dependent fashion. At least one dose and usually two or three doses of each of these drugs produced stimulus control of responding comparable to the PCP training dose. Furthermore, for all six compounds, the highest doses given produced stimulus control of responding greater than the PCP training dose. The slopes of all of the dose-response curves were similar.

All of the compounds tested had comparable effects on rate of responding. For each compound, there was a relatively low dose which produced a slight although not statistically significant increase in overall response rates. These findings are consistent with other reports of increases in low rates of schedule-controlled responding with low doses of PCP in squirrel monkeys [7, 8, 9]. For the most part, these response rate increasing doses produced less than 50% drug-lever appropriate responding. It is possible that this is due to some behavioral activity of these compounds at doses even lower than those producing discriminative stimuli. It is also possible that using a lower training dose of PCP, generalization would be seen at these response rate increasing doses. Higher doses of all compounds suppressed operant responding in a dose-dependent fashion. The slopes for the descending limb of the dose-response curves were similar for all six drugs.

For all of the compounds tested, the ED50 value for response rate suppression was three to five times larger than the ED50 value for drug-lever appropriate responding. Doses could be found for all compounds which produced 70 to 100 percent drug-lever appropriate responding without decreasing response rates to below saline control levels. This indicates that the drug discrimination paradigm may be a very sensitive method to assay the behavioral activity of a PCP-like compound.

The gross observable effects of high doses of all six drugs were also similar. Excessive salivation, nystagmus and an inability to maintain balance on a perch when returned to the home cage were the most notable features. Balster and Chait [2,3] have reported comparable effects in primates after PCP administration.

Our data support most of the previous work in both *in vivo* and *in vitro* systems in showing pharmacological similarities between the five analogues tested here and PCP. In agreement with the study by Brady *et al.* [5], we found that these analogues had similar observable effects on primates, as well as similar effects on schedule-controlled performance. The present study also supports the previous drug discrimination work done with PCP in a drug vs. saline task. In addition, PCP, PCE and TCP have been shown in several studies [17, 18, 19, 21, 22, 23, 24, 28] to have both anticholinergic and anticholinesterase activity using receptor binding and bioassay procedures.

One interesting discrepancy between our findings and those reported in the literature lies with the study by Gehrmann and Killam [12] where they report a qualitative difference between the EEG changes produced by PHP and those produced by the rest of the analogues which they tested. Neither our study nor any in the literature indicates that the spectrum of action of PHP differs from that of PCP in a variety of pharmacological assays.

There is some disagreement in the literature concerning the potency of the analogues relative to PCP. Most studies find PCM and ketamine to be approximately one fifth to one tenth as potent as PCP. There also seems to be general agreement that PCP, PHP and TCP are roughly equipotent. However, conflicting results have been obtained concerning the potency of PCE relative to PCP. Several investigators using motor effects in mice [1, 16, 24] have reported that PCE is two to three times more potent than PCP. Jarbe *et al.* [15] reported that PCE was somewhat more potent than PCP and Shannon [26] found PCE to be nearly six times more potent than PCP in the discriminative stimulus paradigm using rats. On the other hand, in the present study PCE and PCP were found to be roughly equipotent in producing drug-lever appropriate responding. This is similar to the results of a previous study in rhesus monkeys [5] in which PCP and PCE were found to be roughly equipotent in suppressing response rates maintained under a fixed-interval schedule. Chen [10] also found PCE and PCP to be equipotent in producing catalepsy in pigeons. While the reason for these discrepancies is not clear, it could reflect a difference in the

biodispostion of PCE in rodents compared to primate species. Kalir *et al.* [16] found that a higher percentage of the injected amount of drug was found in the brain of mice after PCE administration than after PCP administration, but similar studies have not yet been done with primates.

One last point concerns the use of primates in drug discrimination procedures. There have been relatively few reports using squirrel monkeys in drug discrimination studies [14,29]. Woolverton and Trost [29] found that squirrel monkeys could discriminate doses of cocaine 100-fold less than those used in many rat discrimination studies with cocaine. The training dose of PCP used in this study was 20 times less than that used in rat studies [15, 20, 26]. This sensitivity coupled with the differences in the behavioral activity of the dissociative anesthetics between primates and rodents makes it especially important to assay the activity of PCP and its analogues in primates.

In conclusion, PCP was found to produce stimulus control over responding in squirrel monkeys in a dose-dependent manner. The drug discrimination paradigm provides a very sensitive measure of PCP's behavioral activity in so far as drug-lever appropriate responding was maintained at doses which produced no observable effects. The five structural analogues of PCP which were tested all produced dose-dependent PCP appropriate responding and were similar to PCP in their observable effects as well as their effects on overall response rates.

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